IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDING, LTD. and H. LUNDBECK A/S,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 03-891-JJF
IVAX PHARMACEUTICALS, INC., and CIPLA LTD.,	:	
Defendants.	:	

Melanie K. Sharp, Esquire and Andrew Lundgren, Esquire of YOUNG CONAWAY STARGATT & TAYLOR, Wilmington, Delaware.
Of Counsel: John M. Desmarais, Esquire; Peter J. Armenio, Esquire; Gerald J. Flattman, Jr., Esquire and Maxine Y. Graham, Esquire of KIRKLAND & ELLIS LLP, New York, New York.
Attorneys for Plaintiffs.

Richard D. Kirk, Esquire of THE BAYARD FIRM, Wilmington, Delaware.
Of Counsel: Jeffrey S. Ward, Esquire; Thomas P. Heneghan, Esquire; Shane A. Brunner, Esquire; Edward J. Pardon, Esquire and Charlene L. Yager, Esquire of MICHAEL BEST & FRIEDRICH LLP, Madison, Wisconsin.
Attorneys for Defendants.

O P I N I O N

July 13, 2006
Wilmington, Delaware

Farnan, District Judge.

This action was brought by Plaintiffs, Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd. and H. Lundbeck A/S (collectively, "Plaintiffs"), against Defendants Ivax Pharmaceuticals, Inc. ("Ivax") and Cipla Ltd. ("Cipla") (collectively, "Defendants") alleging infringement of U.S. Patent No. Re. 34,712 (the "'712 patent") based on IVAX's submission of Abbreviated New Drug Application ("ANDA") 76-765 to the Food and Drug Administration and CIPLA's role in assisting IVAX with the submission of ANDA 76-765 and serving as a future importer and manufacturer of the generic product contemplated by ANDA 76-765. For purposes of this action, the parties have stipulated to a specific claim construction for the primary disputed term in the '712 patent. Based on this agreed upon claim construction, the parties have further stipulated that the proposed generic products defined by ANDA 76-765 infringe claims 1,3,5,7 and 9 of the '712 patent. (PTX 189). The parties have also stipulated that Defendants' process for making the proposed generic products will infringe claim 11 of the '712 patent. (PTX 782).

Because the parties have stipulated to infringement for purposes of this litigation, the only issues remaining for adjudication by the Court are Defendants' counterclaims of invalidity and unenforceability. Specifically, Defendants seek a declaratory judgment that (1) claim 1 of the '712 patent is

invalid as anticipated under 35 U.S.C. § 102; (2) claims 1,3,5,7,9 and 11 of the '712 patent are invalid as obvious under 35 U.S.C. § 103; and (3) claim 11 of the '712 patent is invalid as an improperly broadened reissued claim under 35 U.S.C. § 251. In addition, Defendants seek a declaratory judgment that the '712 patent is unenforceable due to inequitable conduct.

This action arises under the patent laws of the United States, Title 35 of the United States Code and the Abbreviated New Drug Application provisions of the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j). Accordingly, the Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338.[1]

The Court conducted a five day bench trial on the issues presented by the parties. This Opinion constitutes the Court's findings of fact and conclusions of law on Defendants' counterclaims of invalidity and unenforceability.

BACKGROUND

I. The Parties

Plaintiff H. Lundbeck A/S ("Lundbeck") is a Danish corporation with a principal place of business in Copenhagen,

---

[1] Cipla reiterates its contention that the Court does not have jurisdiction over it; however, the Court has denied Cipla's Motion To Dismiss Amended Complaint For Lack Of Subject Matter Jurisdiction (D.I. 296). Accordingly, for the reasons discussed in the Court's previous decision, the Court concludes that subject matter jurisdiction exists as to Cipla.

Denmark. (D.I. 526, Attachment 1 "Admitted Facts" at ¶ 3, 35). Lundbeck is the sole owner of the '712 patent. Plaintiff Forest Laboratories Holding, Ltd. ("Forest Holding") is a Bermudian corporation with a principal place of business in Hamilton, Bermuda.[2] (D.I. 536 at 2; Admitted Facts at ¶ 1-2). Forest Holding is the exclusive licensee of the '712 patent. (Admitted Facts at ¶ 36). Plaintiff Forest Laboratories, Inc. ("Forest Laboratories") is a Delaware corporation with a principal place of business in New York City. (Admitted Facts at ¶ 1-2). Forest Laboratories holds New Drug Application (NDA) 21-323 on LEXAPRO® brand escitalopram oxalate products. (Admitted Facts at ¶ 37).

Defendant Ivax is a Florida corporation with a principal place of business in Miami, Florida. (Admitted Facts at ¶ 5). Ivax submitted ANDA 76-765 seeking approval to market generic tablets containing 5, 10 or 20 milligrams of escitalopram oxalate. (Admitted Facts at ¶ 39). Defendant Cipla is an Indian corporation with a principal place of business in Mumbai, India. (Admitted Facts at ¶ 6). Cipla provided information to IVAX that was included in the submission of ANDA 76-765 to the FDA, and under ANDA 76-765, Cipla will manufacture the escitalopram oxalate used in the proposed generic drugs. (Admitted Facts at ¶

---

[2] Forest Holding was initially an Irish corporation with the name Forest Laboratories Ireland, Ltd. ("Forest Ireland"). By stipulation, the parties changed all references to Forest Ireland to Forest Holding. (D.I. 536).

42).

II. The Patent Generally

The '712 patent is a reissue of U.S. Patent No. 4,943,590 (the "'590 patent"). (Admitted Facts at ¶ 12). The '590 patent originally issued on July 24, 1990. (Admitted Facts" at ¶ 13). On August 30, 1994, the '712 patent was issued. (Admitted Facts at ¶ 9; DTX 1). The '712 patent is entitled "Pharmaceutically Useful (+)-1-(3-dimethylaminoproply)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile And Non-Toxic, Acid Additional Salts Thereof." (DTX-1). The named inventors of the '712 patent are Klaus P. Bøgesø and Jens K. Perregaard. The '712 patent covers substantially pure (+)-citalopram, also known as "S-citalopram" or "escitalopram," in the oxalate salt form, which is the active ingredient in LEXAPRO®, an antidepressant drug, from the class of compounds known as selective serotonin reuptake inhibitors ("SSRIs").

The '712 patent is set to expire on June 8, 2009; however, Lundbeck has timely requested a patent term extension of 827 days. (Admitted Facts at ¶ 14, 16). Lundbeck's request for an extension has not been challenged, and therefore, the '712 patent will not expire until September 13, 2011. In addition to this extension period, LEXAPRO® brand escitalopram oxalate products covered by the '712 patent are subject to a pediatric extension of six months. (Admitted Facts at ¶ 15). Thus, generic versions

of the LEXAPRO® products covered by the '712 patent are precluded from being marketed in the United States until March 13, 2012. (Admitted Facts at ¶ 18).

DISCUSSION

I. Whether The '712 Patent Is Invalid

Once a patent is issued by the United States Patent and Trademark Office ("PTO") it is cloaked with a presumption of validity. 35 U.S.C. § 282. This presumption of validity also applies to reissued patents. 35 U.S.C. § 252. To overcome this presumption, the party challenging the patent must demonstrate by clear and convincing evidence that the patent is invalid. U.S. Gypsum Co. v. Nat'l Gypsum Co., 74 F.3d 1209, 1212 (Fed. Cir. 1996).

A. Whether Claim 1 of the '712 Patent Is Anticipated

Pursuant to 35 U.S.C. § 102(g), a patent is invalid as anticipated if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent. . . ." To anticipate a patent, a prior printed publication must contain each and every limitation of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the claimed invention without undue experimentation. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed. Cir. 2000).

1. Whether the Smith reference contains each element of claim 1 of the '712 patent

Defendants contend that claim 1 of the '712 patent is anticipated by Donald F. Smith, The Stereoselectivity of Serotonin Uptake in Brain Tissue and Blood Platelets: The Topography of the Serotonin Uptake Area, Neuroscience and Behavioral Reviews, Vol. 10, pp. 37-46 (1986) (DTX 871) ("Smith" or the "Smith reference"). Specifically, Defendants cite to a portion of Smith which provides:

> [C]italopram . . . is a racemic drug with potent inhibitory effect on 5-HT [serotonin] uptake. Although effects of the individual enantiomers of citalopram have never been studied, the model predicts that the (R)-enantiomer is far more potent that the (S)-enantiomer as a 5-HT uptake inhibitor. Thus, the present model can be tested by determining whether these predications are correct.

(DTX 871 at DS000200) (internal citations omitted).

To contain each and every element of the claimed invention, a prior art printed publication need not recite the elements of the patent claim in language identical to the language used in the claim, so long as the reference teaches the entirety of the invention. Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 716 (Fed. Cir. 1984). "Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice or processes disclosed in references." W.L. Gore &

Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1554 (Fed. Cir. 1983); see also Mentor H/S, Inc. v. Med. Device Alliance, Inc., 244 F.3d 1365, 1376 (Fed. Cir. 2001) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish anticipation.]"). In addition, references that have the same general features as the invention do not anticipate the invention, and one skilled in the art cannot supply missing elements through his or her knowledge. Stated another way, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991). Whether a step or element is expressly or inherently disclosed in a prior art reference is a question of fact. Tegal Corp. v. Tokyo Electron Am., Inc., 257 F.3d 1331, 1345-1346 (Fed. Cir. 2001).

Claim 1 of the '712 patent claims substantially pure (+)-citalopram which the parties have agreed, for purposes of this litigation, means "(+)-citalopram with a 90% enantiomeric enrichment ("e.e.") or, said another way, at least 95% pure (+)-citalopram with no more than 5% (-)-citalopram. (D.I. 526, Tab 1 at ¶ 34). Defendants contend that Smith discloses substantially pure (+)-citalopram as defined by the parties' stipulation, because it discloses the separation of racemic citalopram into

its individual enantiomers, the (R)-enantiomer and the (S)-enantiomer. Defendants further contend that one of ordinary skill in the art would know that there are only two enantiomers of citalopram, and therefore, one of these two forms would necessarily correspond to (+)-citalopram and the other would necessarily correspond to (-)-citalopram.

Plaintiffs contend that the disclosure of racemic citalopram does not necessarily anticipate the individual enantiomers of citalopram; however, Defendants' argument that the Smith reference contains each element of claim 1 of the '712 patent is not premised on the disclosure of racemic citalopram, but rather on the Smith reference's express disclosure of the individual enantiomers of citalopram. Although Smith refers to each enantiomer of citalopram generally, the Court is not persuaded that Smith discloses substantially pure (+)-citalopram as defined by the parties in this litigation. Smith only discloses the chemical structure of (R)-citalopram and does not disclose the chemical structure of (S)-citalopram, which corresponds to (+)-citalopram. In addition, Smith does not disclose anything with regard to the purity of the (S)-enantiomer when it mentions that enantiomer, and the Court cannot presume that the disclosure of (R)-citalopram, individually and not in any mixture, necessarily discloses substantially pure (S)- or (+)-citalopram. In these circumstances, the Court cannot conclude that Smith discloses the

entirety of the claimed invention. Accordingly, the Court concludes that Defendants have not established by clear and convincing evidence that the Smith reference contains each and every limitation of the claimed invention.

2. Whether the Smith reference is enabled such that it anticipates claim 1 of the '712 patent

However, even if the Court concludes that the Smith reference discloses (+)-citalopram as defined by the parties, the Court concludes that Defendants have failed to establish that the Smith reference is enabled. Even if a claimed invention is sufficiently disclosed in a prior art publication, the publication will not anticipate the claim if the prior art publication is not enabling. Novo Nordisk Pharms. v. Bio-Technology Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005). For purposes of Section 102, a prior art publication is enabling if "one of ordinary skill in the art could practice the invention without undue experimentation." Elan Pharms., Inc. v. Mayo Found. for Med. Educ & Research, 346 F.3d 1051, 1055 (Fed. Cir. 2003). The determination of what amount of experimentation is considered "undue," is made from the point of view of an experienced person in the field of the invention. Id. Factors relevant to determining whether experimentation is undue such that the reference is not enabled include: (1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working examples; (4) the nature

of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

An invention disclosed in a publication need not have been actually made to be considered enabled; however, "failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling." In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985). Further, additional prior art references may be used to show that an anticipatory reference is enabled, so long as those references are not used to meet any missing claim elements. Bristol-Meyers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001).

The Federal Circuit has also recognized a presumption that prior art patents are enabled. However, the presumption of enablement has not been expressly extended to prior art printed publications, although the Federal Circuit has suggested that "by logical extension" such a presumption "might also apply to prior art in printed publications as well . . ." Amgen Inc. v. Hoecht Marion Roussel, Inc., 314 F.3d 1313, 1355 & n.22 (Fed. Cir. 2003).[3] Whether a prior art reference is enabling is a question

---

[3] The Court has been unable to locate any case law resolving the question of the burden of proof on enablement in the case of prior art, non-patent, printed publications. In an

of law premised on underlying factual findings. Novo Nordisk, 424 F.3d at 1355.

a. The level of one of ordinary skill in the art

For purposes of determining the validity of the '712 patent, the parties agree that the Court must consider a person of ordinary skill in the art as of June 14, 1988. (D.I. 605 at 6; D.I. 602 at 7). The parties' experts also agreed that the pertinent art for the '712 patent is medicinal chemistry (Danishefsky Tr. 1221:22-1222:15; Trost Tr. 242:2-11); however, the parties' experts diverged on the amount of education and/or experience required for one to be considered of ordinary skill level in the art of medicinal chemistry. Plaintiffs' expert, Dr.

---

unpublished decision, the United States District Court for the District of New Jersey declined to apply the presumption of enablement discussed in Amgen to non-patent, printed publications absent further guidance from the Federal Circuit. See e.g. Matsushita Electric Industrial Co. v. Samsung Electronics Co., Ltd., 2006 WL 1794768, *4-5 (D.N.J. June 26, 2006). However, some courts have applied the presumption. See Novo Nordisk, 424 F.3d at 1356 (discussing the district court's opinion and recognizing that the district court applied the Amgen presumption stating that "the court did not rely solely on the Amgen presumption in finding that the 1981 Pavlakis article was enabled," but declining to expressly determine whether the Amgen presumption applied to a prior art printed publication). In any event, courts have recognized that if the burden shifts to the patentee to demonstrate nonenablement, the burden is not as high as the clear and convincing standard needed to demonstrate invalidity. See e.g., Alza Corp. v. Mylan Laboratories, Inc., 388 F. Supp. 2d 717, 734 & n.11 (N.D.W. Va. 2005). This lower evidentiary burden suggests to the Court that even if the patentee is required to present some evidence of nonenablement, the burden still rests on the party asserting invalidity to ultimately demonstrate by clear and convincing evidence that the prior art is enabled.

Danishefsky, opined that a person of ordinary skill in the art would have had a Bachelor's degree and ten years of training, or a Master's degree and five years of training, or a Ph.D. and two years of training. (Danishefsky 1221:22-1223:14). In contrast, Defendants' experts, Dr. Trost and Dr. Ward, opined that one of ordinary skill in the art would have a Ph.D., with an emphasis on synthetic organic chemistry or medicinal chemistry, and a number of years of experience in the pharmaceutical industry. (Ward Tr. 76:1-6; Trost Tr. 188:2-11). However, both Dr. Trost and Dr. Ward opined that a person with a Master's or Bachelor's degree would satisfy the level of ordinary skill in the art, if that person had enough practical experience to put them on par with a person who had a Ph.D. (Ward Tr. 76:15-77:6; Trost Tr. 189:21-190:12).

The Federal Circuit has identified several factors that may be used in determining the level of ordinary skill in the art, including but not limited to (1) the educational level of the inventor; (2) the types of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field. See e.g. Envtl. Designs Ltd. v. Union Oil Co. of Calif., 713 F.2d 693, 696-697 (Fed. Cir. 1983). These factors need not be present in every case and certain factors may be more

predominate in some cases than in others. In the Court's view, Dr. Danishefsky's opinion concerning the level of one of ordinary skill in the art is more consistent with the factors identified by the Federal Circuit for making this assessment. Accordingly, the Court concludes that a Ph.D. is not required for one to be considered a person of ordinary skill in the art of medicinal chemistry as of June 1988.

b. Whether one of ordinary skill in the art could practice the invention without undue experimentation

The parties' experts agreed that the Smith reference itself does not disclose any methods for separating citalopram into its individual enantiomers or for producing substantially pure (+)-citalopram. (Danishefsky Tr. 1227:2-21; Smith Tr. 1150:14-17; Trost Tr. 197:1-4). Indeed, Dr. Smith himself testified that he did not know how to separate the enantiomers of citalopram when he authored the Smith reference, and he did now know of anyone anywhere in the world who had accomplished the separation of citalopram. (Smith Tr. 1149:17-19, 1150:10-13, 1201:17-1202:21, 1205:17-1206:23). Thus, the Smith reference provides no guidance as to how to obtain substantially pure (+)-citalopram, and therefore, the Court concludes that the Smith reference, standing alone, is not enabling.

Although Smith does not disclose how to separate citalopram into its enantiomers, Defendants contend that at least three

reliable methods existed in the prior art as of June 14, 1988, by which a person of ordinary skill in the art could have obtained substantially pure (+)-citalopram without undue experimentation: (1) chiral High Performance Liquid Chromatography ("HPLC"), (2) diastereomeric salt formation, and (3) diastereomeric formation of covalent compounds. The Court has considered the evidence presented by the parties as to each of these methods and concludes that Plaintiffs have demonstrated, by at least a preponderance of the evidence, that undue experimentation would have been required to successfully use these methods to obtain (+)-citalopram. In the Court's view, Plaintiffs' evidence is sufficient to rebut any presumption of enablement that might apply as a result of the Amgen decision. Having come forward with sufficient evidence to rebut the presumption of enablement, the Court further concludes that Defendants have failed to carry their ultimate burden of demonstrating invalidity by clear and convincing evidence. As Defendant's expert, Dr. Trost acknowledged, no one had published any methods for separating the enantiomers of citalopram as of June 14, 1988 (Trost Tr. 248:13-21), and therefore, there were no working examples or specific guidance available to anyone attempting to accomplish this separation. Indeed, with respect to chiral HPLC in particular, the Court notes that as late as 2002, the separation of citalopram using chiral HPLC was still considered a "hot

application" for which many sought assistance. (PTX 118, Tab 32; Lazarowych Tr. 354:17-355:14).

In addition to the lack of specific guidance or working examples of the separation of citalopram in the prior art using any method, Plaintiffs also presented credible evidence that chiral HPLC was considered a relatively new and unpredictable technique in 1988. (Pochapsky Tr. 1327:3-16, 1342:4-15, 1343:20-1345:5. 1346:18-1347:14; Danishefsky Tr. 1234:12-1235:23; Gundertofte Tr. 1083:9-1084:15). Plaintiffs' expert, Dr. Pochapsky, worked in the laboratory of Dr. Pirkle, who is considered the founder of the field of chiral HPLC, for about five years and conducted numerous HPLC experiments. (Pochapsky Tr. 1318:7-13, 1321:4-21; PTX 219). Dr. Pochapsky along with Dr. Danishefsky, the only witness qualified by the Court as an expert in the field of medicinal chemistry, explained that chiral HPLC was primarily an analytical method in 1988, and a medicinal chemist of ordinary skill in the art would not have been facile in the use of chiral HPLC. (Pochapsky Tr. 1343:20-1345:24, 1350:17-1351:6; Danishefsky Tr. 1237:16-1238:15). According to Plaintiffs' experts, when chiral HPLC worked, it allowed only the detection of enantiomers in a racemic mixture, and did not allow for their collection. As a result, the Court is persuaded by the testimony of Plaintiffs' experts that chiral HPLC was not a predictable or reliable method for the separation of citalopram,

and in fact, would have been the least likely method used by one skilled in the art of medicinal chemistry for the resolution of citalopram into its enantiomers. (Danishefsky Tr. 1238:5-15).

The Court acknowledges that Defendants presented the contrary testimony of Drs. Ward and Trost; however, the Court is not persuaded by the testimony of these experts and credits the testimony of Plaintiffs' experts over the testimony of the experts presented by Defendants. First, Dr. Ward's perspective is not the perspective of one of ordinary skill in the art of medicinal chemistry. Dr. Ward is not a medicinal chemist and his expertise lies in chiral HPLC. (Ward Tr. 129:6-23). Because Dr. Ward did not testify consistently with the standard adopted by the Court for one of ordinary skill in the art, the Court concludes that his testimony was of limited value in determining whether a medicinal chemist of ordinary skill in June 1988, could have used chiral HPLC for the resolution of citalopram. As for Dr. Trost, the Court is also not persuaded by his testimony as compared with the testimony of Plaintiffs' experts and finds his testimony to be more theoretical in nature and contrary to his practical experiences. For example, Dr. Trost testified that as of June 14, 1988, chiral HPLC would have been the first choice method for one of ordinary skill in the art seeking to resolve citalopram into its constituent enantiomers. However, Dr. Trost testified that, through March 2005, he himself had never used

chiral HPLC to obtain substantially pure enantiomers. (Trost Tr. 252:19-253:1, 247:8-10). Indeed, Dr. Trost did not remember referring to the use of chiral HPLC for any purpose in his publications prior to 1997, and Dr. Trost admitted that chiral HPLC was not even listed as one of the "Enantioselective Strategies" for obtaining enantiomers in a paper he authored. (Trost Tr. 249:8-252:18; PTX 74).

The unpredictable nature of chiral HPLC as a technique for resolving citalopram is also demonstrated by the quantity of experimentation of others and their lack of real world successes in using chiral HPLC to resolve citalopram and similar compounds during the relevant time. For example, even Defendants' expert, Dr. Ward, who is significantly accomplished in the area of chiral HPLC, testified that he repeatedly tried and failed to separate a compound structurally similar to citalopram during the relevant time frame. (Ward Tr. 171:9-173:7; PTX 125). Dr. Ward acknowledged that significant challenges existed to separating certain compounds and achieving optically pure isomers and that slight differences in the chemical structure of the compound under consideration, along with numerous variables such as derivitazation problems, solvent choice, temperature, the type of overall mobile phase in light of the additives and solvents used, and the Ph could prevent the ultimate separation of a compound like citalopram using chiral HPLC. (Pochapsky Tr. 1333:22-

1339:9, 1341:11-1342:15; Ward Tr. 141:5-19; DTX 919).

Further, the evidence demonstrates that significant obstacles existed with respect to column selection as of June 14, 1988. Defendants' experts testified that one of ordinary skill in the art would have focused on three of 31 available chiral HPLC columns, the Chiracel OD column, the beta-acetylated cyclodextrin column, and Chiral AGP column. Although the prior art Wainer reference may have narrowed this selection to 12 of the 31 columns, the Court is still convinced that the ultimate selection of the three column identified by Defendants would have taken a great deal of experimentation in 1988. In addition to the deficiencies and problems that existed with respect to each of the three columns identified by Defendants, two of the three columns were actually contraindicated by Wainer and another prior art paper, the Johns paper, making their selection by one skilled in the art even less likely at the relevant time, and more likely the result of extraordinary experimentation. (Ward Tr. 154:10-156:16, 164:24-166:16; DTX 716; DTX 913)

Defendants also direct the Court to the work of Dalton Labs and Dr. Lazarowych for the proposition that one skilled in the art could have achieved the separation of citalopram in June 1988 using chiral HPLC. However, Dr. Lazarowych never personally used chiral HPLC and admitted that she consulted literature from 1995, 1996 and 2001 before selecting the columns that Dalton Labs

ultimately used to achieve the separation of citalopram using chiral HPLC. (Lazarowych Tr. 314:3-319:22; 309:3-23; PTX 118 at Tabs 10, 23, 38). In addition, Dr. Lazarowych testified that Dalton used columns and methods contrary to the teachings of prior art papers like the Wainer and Johns papers, but consistent with papers like the 1995 Rochat paper and the 2001 Carlsson paper. (Lazarowych Tr. 319:23-327:18; 335:3-336:9; Ward Tr. 156:3-16). Further, the actual columns used by Dalton were either not available in 1988, or had been substantially improved since that time. (Lazarowych Tr. 331:12-334:14, 338:18-343:3, 326:14-330:17; Pochapsky Tr. 1367:15-1373:13, 1426:21-1427:22; Ward Tr. 143:19-150:12, 150:19-153:1; Trost Tr. 146:1-147:2; DTX 947). Accordingly, the Court concludes that the testimony of Dr. Lazarowych and the work of Dalton Labs is irreparably tainted with the benefits of hindsight, and therefore, the Court concludes that it is not credible for purposes of determining whether one of ordinary skill in the art of medicinal chemistry could have separated citalopram into substantially pure (+)-citalopram in June 1988.

In contrast to the theoretical and hindsight testimony of Defendants' experts, Plaintiffs presented the testimony of individuals, like Dr. Smith and Mr. Klaus Gundertofte, who actually attempted to use chiral HPLC to achieve the separation of citalopram during the relevant time. For example, in 1985,

Dr. Smith, in collaboration with Dr. Pirkle, tried to separate citalopram using chiral HPLC, but their collective efforts failed. (Smith Tr. 1151:19-1152:13, 1153:21-1162:24, 1168:17-20). Similarly Mr. Gundertofte and his team of chemists at Lundbeck unsuccessfully tried to separate citalopram into its enantiomners using chiral HPLC for a period of two years. (Gundertofte Tr. 1085:17-1093:1, 1108:14-17, 1109:22-1110:1; PTX 1155; PTX 214A at FL9110-9111; PTX 201 at FL8602). Dr. Danishefsky and his laboratory also tried to resolve medicinal compounds with HPLC during the mid-1980s without success. (Danishefsky Tr. 1238:16-1239:7).

In addition to the significant amount of failed experimentation with chiral HPLC during the relevant time, the Court also concludes that the other methods of separation identified by Defendants could not have resolved citalopram without undue experimentation. Dr. Bøgesø, the inventor of the '712 patent, conducted numerous experiments attempting to resolve citalopram through the formation of diastereomeric salts using chiral acid; however, Dr. Bøgesø's efforts were unsuccessful. (Bøgesø Tr. 897:16-898:18, 911:4-934:4, 974:22-975:18; PTX 1076-1078, 1080). Dr. Bøgesø ultimately attempted separation using the Diol Intermediate method claims in the '712 patent, but he explained that he approached this method as a last resort, because it required the development of new chemistry to cyclize

the Diol Intermediate while retaining any enantiomeric purity. (Bøgesø Tr. 944:13-960:24, 966:19-24, 967:3-9; Danishefsky Tr. 1240:6-1242:2, 1243:1-1245:6). Indeed, even Defendants' expert, Dr. Trost, admitted that one of ordinary skill in the art would have attempted to resolve citalopram itself, rather than try to obtain an enantiomerically pure Diol Intermediate and then develop an enantioconserving cyclization method. (Trost Tr. 201:3-9). As Dr. Danishefsky pointed out, the Diol Intermediate method was laden with risks and chemists would be reluctant to resolve an intermediate, rather than a final product, because the resolved intermediate could re-racemize during the latter part of the synthesis. (Danishefsky Tr. 1240:6-1245:6; Bøgesø Tr. 945:20-946:7, 957:8-960:24).

Further, the development of the enantioconserving ring closure for the Diol Intermediate was not possible using the methods of the prior art patent invented by Dr. Bøgesø, U.S. Patent No. 4,650,884 (the "'884 patent"), which disclosed a process for making racemic citalopram by starting with the precursor, diol compound. (Danishefsky Tr. 1242:3-24). As Defendant's expert, Dr. Trost, noted the ring closure reactions depicted in the '884 patent and other prior art references would have destroyed any enatiomeric purity obtained with the Diol Intermediate. (Trost Tr. 266:21-268:21). Moreover, Dr. Trost could not point out a single prior art reference showing the type

of reaction that would have been needed to convert any enantiomerically pure Diol Intermediate into substantially pure (+)-citalopram. (Trost Tr. 274:20-275:8). To the extent Dr. Trost testified otherwise, the Court concludes that his testimony was riddled with hindsight. (Trost Tr. 243:24-244:5). Accordingly, the Court is persuaded that the separation of citalopram using the methods identified by Defendants could not have been achieved without undue experimentation.

In sum, the Court concludes that the Smith reference is not enabled as to the separation of the enantiomers of citalopram. The lack of guidance in the prior art and the real world failure of others coupled with the risks and variables involved with each of the separation techniques demonstrates that one skilled in the art of medicinal chemistry as of June 14, 1988, would not have been able to obtain substantially pure (+)-citalopram without undue experimentation. Accordingly, the Court concludes that Defendants have not demonstrated by clear and convincing evidence that the Smith reference anticipates claim 1 of the '712 patent.

B. Whether Claims 1, 3, 5, 7, 9 and 11 of the '712 Patent Are Obvious

In pertinent part, 35 U.S.C. § 103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art . . ." 35 U.S.C. § 103.

Though ultimately a question of law, obviousness is predicated upon several factual inquiries. Pfizer, 405 F. Supp. 2d at 516 (citing Richardson-Vicks v. UpJohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997)). Specifically, the trier of fact must consider four issues: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid, and unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). As with anticipation, the party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Brown & Williamson Tobacco Co. v. Phillips Morris Inc., 229 F.3d 1120, 1124 (Fed. Cir. 2000); C.R. Bard, Inc. v. M3 Systems, 157 F.3d 1340, 1351 (Fed. Cir. 1998).

Defendants contend that the asserted claims of the '712 patent are prima facie obvious in light of U.S. Patent No. 4,136,193 (the "'193 patent"). The '193 patent claims racemic citalopram and discloses its use as an antidepressant. Defendants contend that (+)-citalopram is structurally similar to

racemic citalopram and is used to treat the same condition as racemic citalopram, and therefore, one skilled in the art would have been motivated to make the claimed compound.

In Pfizer, the Court considered the question of whether a patent that claimed a racemate rendered obvious a second patent which claimed the enantiomer of that racemate. In resolving this issue, the Court recognized that "courts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate or render the individual isomers of the racemate obvious." 405 F. Supp. 2d at 519. The Court went on to determine specifically whether one skilled in the art of medicinal chemistry as of July 1989, a year later than the priority date in this case, would have been motivated to resolve the racemate atorvastatin into its individual enantiomers. Id. at 517. The Court found that "the prior art indicates that the motivation at the time was to develop racemates and make structural changes to the compounds to increase their activity, not to resolve those racemates into individual isomers." Id.

Defendants in this case have not demonstrated that the state of the art was any different in 1988 with respect to citalopram than it was in 1989 with respect to atorvastatin. According to Dr. Danishefsky, whose testimony the Court credits over the

testimony of Defendants' experts, a person of ordinary skill in the art of medicinal chemistry seeking to discover a new SSRI would have been motivated to design a new compound, rather than engage in the time consuming and unpredictable effort of resolving citalopram into its enantiomer. (Danishefsky Tr. 1228:12-1229:6). Indeed, even Defendants' experts acknowledged that the resolution of racemic compounds is difficult to achieve in today's world, and the activity of a particular enantiomer could not be known until it was actually separated and tested. (Trost 253:18-22; Barker Tr. 401:16-406:21). In fact, the conventional wisdom in the scientific community in 1988 was that one enantiomer of a racemate was likely to have at most two times the potency of the racemic mixture from which it was derived, while the other enantiomer would be largely inactive.[4] (See e.g., Danishefsky Tr. 1308:10-13; Trost 261:23-262:14; Lader Tr. 1511:14-1512:9). Given the significant difficulties identified by Dr. Danishefsy in resolving citalopram and the unpredictable nature of the separation techniques and separation results of racemates in general[5], as well as the minimal gains that were

---

[4] See e.g. Pfizer, 405 F. Supp. 2d at 517 ("The resolution of reacemates into their individual isomers yielded, at best, an expectation of a two-fold increase in activity. This modest increase in activity was offset by the difficulty and complexity of the resolution process . . .").

[5] The unpredictable nature of the separation of racemic compounds is also illustrated by the separation of fluoxetine (Prozac) and paroxetine (Paxil) in the late 1980s. Despite

typically predicted by the resolution of racemates into their constituent enantiomers (Danishefsky Tr. 1228:12-1231:12, 1235:24-1237:15, 1306:24-1309:16), the Court concludes that Defendants have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.

In addition, the Court is further persuaded that a person skilled in the art seeking such a resolution would not have a reasonable expectation of success without undue experimentation. As the Court recognized in the context of its discussion of anticipation, resolution of citalopram was a challenging and risky endeavor that required significant experimentation to yield positive results. (Danishefsky Tr. 1234:12-1240:5, Bøgesø Tr. 976:13-977:3). The Court's conclusion in this regard is supported by the lack of documented successes in achieving this resolution, as well as by the numerous failures of others to obtain this separation by traditional methods. (See e.g., Bøgesø

---

predictions to the contrary, the separation of paroxetine actually reflected a 25 fold to 250 fold increase in potency associated with the plus enantiomer. However, these same results did not hold true with fluoxetine, despite similarities between it and paroxetine. In the case of fluoxetine, researchers had predicted that most of the therapeutic activity would reside in a single enantiomer; however, when actually separated, the enantiomers were reported to have nearly equal potency. Researchers also learned that the R-enantiomer of fluoxetine was cardiotoxic when administered alone, but demonstrated no toxicity when administered as part of the racemate. (Barker 412:22-421:10).

Tr. 911:4-932:13, 933:12-934:4, 972:3-9, 974:22-975:8; PTX 1076-1078).

Defendants also contend that the separation method set forth in claim 11 of the '712 patent using the Diol Intermediate is obvious in light of the combination of several prior art references including the '193 patent in combination with the '884 patent and/or the knowledge of available separation techniques of diastereomeric salt formation and diastereomeric covalent compound. The Court disagrees with Defendant's assertion. First, the Court is not persuaded by the testimony of Dr. Trost on this issue. Dr. Trost failed to demonstrate any motivation for one skilled in the art to combine the references to which he referred, and the Court is persuaded that the ability of one skilled in the art to combine those references would have required undue experimentation. In addition, the references to which Dr. Trost refers either fail to recognize the difficulties of escitalopram synthesis altogether, or actually demonstrate the difficulties involved in the synthesis further substantiating the Court's conclusion that synthesis using the Diol Intermediate was novel. (Danishefsky Tr. 1260:10-1262:21). Further, none of the articles relied upon by Dr. Trost depict a Mosher ester serving as a leaving group for a ring closure of a Diol Intermediate or an enantioconserving ring closure of a diol containing a tertiary amine to form a tetrahydrofuran as described in the '712 patent,

and both Dr. Danishefsky and Dr. Trost were unaware of any prior art references demonstrating an enantioconserving cyclization reaction of the type needed to convert a tertiary amine like any enantiomerically pure Diol Intermediate into substantially pure (+)-citalopram. (Danishefsky 1260:10-1261:4, 1262:16-1263:6; Trost Tr. 274:20-275:8). Moreover, as the Court discussed in the context of anticipation, it was unknown at the relevant time whether it was possible to resolve the Diol Intermediate in the first place, and then, if resolution was possible, there were significant risks, including the risk of re-racemization and the possibility of a McCloskey-type reaction which would have led to demethylation. (See e.g., Danishefsky Tr. 1243:1-1246:24, 1250:15-1252:3, 1252:6-1257:18). Defendants attempt to minimize this risk suggesting that it was no more than a 10-15% risk; however, as Cipla's DMF documents demonstrate the risk is a real risk, because it occurs during Cipla's manufacturing process. (Danishefsky Tr. 1256:24-1257:18; PTX 18C).

In addition to the absence of prior art covering the claims of the '712 patent, and the lack of motivation to combine the prior art that did exist and was relevant, the Court further finds that the secondary considerations of non-obviousness weigh in favor of the Court's conclusion that the patent is valid. As the Court has discussed at length, the evidence demonstrates numerous failures by others attempting to achieve the separation

of citalopram, and in the Court's view, Defendants have not demonstrated the contrary by clear and convincing evidence.[6] See Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578-79 (Fed. Cir. 1991) ("Nonobviousness is suggested by the failure of others 'to find a solution to the problem which the patent[s] in question purport[] to solve.'").

The Court is also persuaded that Lexapro® has been a commercial success in the market. Demaco Corp. v. F. von Langsdorff Licensing Ltd., 851 F.2d 1387, 1391 (Fed. Cir. 1988) ("The commercial response to an invention is significant in determinations of obviousness, and is entitled to fair weight."). Although Lexapro® was a relatively late entrant into the market of antidepressant drugs, it is being prescribed more often than any other drug in its class. (Rothschild Tr. 1823:24-1825:8; Gelenberg Tr. 570:12-21; Trombetta Tr. 700:9-704:16; PTX 1082-1084). In the twelve months ending in November 2005, Lexapro® sales reached $2 billion, despite the availability of racemic citalopram in generic form at lower prices. (Trombetta Tr.

---

[6] The Court acknowledges that Dr. Bøgesø failed to simultaneously record all of his failed experiments, which impacts his credibility to some extent. However, the Court is not persuaded that this fact entirely negates Plaintiffs' evidence on the failure of others to achieve the separation of citalopram. While all of Dr. Bøgesø's failures may not have been documented, it is also true that no successes were documented until Dr. Bøgesø achieved the method described in the '712 patent. Further, the Court's decisions as to both anticipation and obviousness are based on the weight of all of the criteria used in these tests, and not just on the failure of others.

710:8-712:22). In this regard, Plaintiffs' clinical psychiatry experts, Dr. Anthony Rothschild and Dr. Malcom Lader, explained that Lexapro® is preferred to citalopram despite its increased costs, because Lexapro® has superior efficacy compared with other SSRIs, including citalopram. (See e.g. Lader Tr. 1523:13-1525:3, 1549:15-1550:20, Rothschild Tr. 1811:19-1814:11, 1823:24-1824:13; PTX 390).

Defendants acknowledge the commercial success of Lexapro®, but contend that this success has little to do with the efficacy or superiority of Lexapro® compared with other drugs. In this regard, Defendants' expert, Dr. William Trombetta, testified that the success of Lexapro® is the direct result of an aggressive marketing campaign initiated by Plaintiffs to promote the sale of Lexapro®. However, the Court is not persuaded by Dr. Trombetta's testimony. Dr. Trombetta had no opinion regarding the degree to which sales and prescriptions of Lexapro® are the result of its qualities as an effective drug, and did not consult with any physicians or conduct any surveys demonstrating why doctors choose Lexapro® compared with other drugs. Dr. Trombetta also could not state what percentage of Lexapro® sales are the result of marketing and promotional activities compared with sales related to the efficacy of the drug. In fact, Dr. Trombetta had no opinion regarding the efficacy of Lexapro®, and consistent with the testimony of the clinical experts on both sides that

good physicians are not unduly influenced by marketing efforts, Dr. Trombetta acknowledged that even good marketing tactics cannot sell a bad drug. (Trombetta Tr. 735:17-19; 727:16-735:10).

Further, Plaintiffs have presented numerous studies, as well as the testimony of their experts, that Lexapro® is a superior drug compared with citalopram and with other SSRIs in its class. (PTX 147, 148, 233, 409, 151-152; Lader Tr. 1512:17-1562:4, 1660:24-1665:16; Gelenberg Tr. 626:14-18; Gibbons Tr. 846:5-849:5; Rothschild Tr. 1815:16-23). Specifically, the evidence demonstrates that escitalopram not only performs better than citalopram in treating depression, but that it also has a faster onset of action resulting in earlier benefits to patients. Defendants attempt to lessen the importance of these studies or demonstrate flaws in them, but the Court is not persuaded that the deficiencies pointed out by Defendants are sufficient to clearly and convincingly demonstrate invalidity. Indeed, even Defendants' expert, Dr. Gelenberg, acknowledged the significance of the studies submitted by Plaintiffs publishing one in the Journal of Clinical Psychiatry while he served as editor-in-chief of that publication and publishing a letter about the benefits of citalopram derived from that study in a newsletter that he founded called Biological Therapies and Psychiatry. (See e.g. Gelenberg Tr. 593:19-600:5, 604:15-24, 606:9-18, 611:8-612:13,

617:6-622:21, 634:16-636:21).

Plaintiffs have also shown that the superior clinical properties of escitalopram demonstrated by these studies were unexpected. (Tr. Lader 1550:6-20; 1561:24-1562:4; 1511:1-1516:14; 1499:13-24); In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) (recognizing that a showing of unexpected advantages or superiority of the claimed invention rebuts a prima facie case of obviousness). For example, it had been predicted that an enantiomer of citalopram would have at most a two-fold increase in activity; however, the evidence reveals that escitalopram is at least 100 times more potent that R-citalopram. (PTX 1 at Table 1; PTX 308 at Table 1). In addition, Lexapro® has been approved by the FDA to treat general anxiety disorder, a disease that citalopram has not been approved to treat. (Rothschild Tr. 1813:9-1814:11; compare PTX 32 with PTX 250).

The success of Lexapro® and its benefits compared with other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants, to copy the claimed invention. See Proctor & Gamble Co. v. Paragon Trade Brands, Inc., 989 F. Supp. 547, 594 (D. Del. 1997); Ortho-McNeil Pharms., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 759 (N.D.W. Va. 2004). In the Court's view, the copying of others is particularly telling in this case, because citalopram is currently available as a generic drug. Indeed, citalopram is

sold generically by Defendants, yet Defendants seek to copy and sell Lexapro®. Further, five generic drug manufacturers have sought approval to market generic escitalopram products despite the fact that they are already making or can make generic citalopram.[7] (PTX 737-741; PTX 781). In addition, at least one of these companies has acquiesced to the validity and enforceability of the '712 patent by expressly indicating in its certification that it does not seek FDA approval to market generic escitalopram products prior to the expiration of the '712 patent (PTX 739), and a sixth generic drug manufacturer, Alphapharm, has admitted that the '712 patent is valid and enforceable in the context of settling Plaintiffs' claims against it in this litigation. (D.I. 460 at ¶ 5).

In sum, the Court concludes that Defendants have not demonstrated by clear and convincing evidence that the '712 patent is obvious. The evidence presented by Plaintiffs demonstrates that the patented invention is unprecedented in the prior art and that one skilled in the art would not have been able to make the invention, even if they were motivated to do so, without undue experimentation. Plaintiffs have also persuaded the Court that Lexapro® is a different drug than its generic,

---

[7] In their certifications, these companies challenge another Lundbeck patent, U.S. Patent No. 6,916,941, and not the '712 patent. In the Court's view, this further evidences a tacit admission on the part of these companies that the '712 patent is valid.

racemic counterpart citalopram and that Lexapro® has superior potency and efficacy compared with citalopram and other SSRIs which has resulted in its significant success in the market and the attempts by others to partake in that success by copying Lexapro® for generic sales. In the Court's view, Defendants have not overcome Plaintiffs' evidence by the requisite clear and convincing standard. Accordingly, the Court cannot conclude that the '712 patent is invalid as obvious.

C. Whether Claim 11 of the '712 Patent Is Invalid For Broadening A Reissued Claim

Defendants next contend that claim 11 of the '712 patent is invalid, because it improperly broadened the scope of the claims of the original '590 patent upon which it was based. As originally issued, claim 11 of the '590 patent claimed a method for converting substantially pure (+)-diol intermediate to (+)-citalopram. More than two years after the issuance of the '590 patent, Lundbeck changed claim 11 so that it claimed a means for converting substantially pure (-)-diol intermediate to (+)-citalopram. Defendants contend that the (+) and (-) nomenclatures have specific meanings in organic chemistry, and therefore, that the change from the (+) designation of the diol intermediate to the (-) designation describes a method which is not claimed in the '590 patent and is thus, broader than the claim upon which is was originally based. Defendants further contend that the change made to claim 11 of the '712 patent would

not have been apparent to the public, and therefore, the mistake cannot be considered a typographical error.

In pertinent part, Section 251 provides:

> Whenever any patent is, through error without any deceptive intention, deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent, the Director shall, on the surrender of such patent and the payment of the fee required by law, reissue the patent for the invention disclosed in the original patent, and in accordance with a new and amended application, for the unexpired part of the term of the original patent. No new matter shall be introduced into the application for reissue.
>
> * * *
>
> No reissued patent shall be granted enlarging the scope of the claims of the original patent unless applied for within two years from the grant of the original patent.

35 U.S.C. § 251. This section contemplates reissue to correct one of four defects: (1) an error in the specification, (2) a defective drawing, (3) the original claim was too broad, and (4) the original claim was too narrow. "[T]he purpose of the reissue statute is to avoid forfeiture of substantive rights due to error made without intent to deceive." Scripps Clinic, 927 F.2d 1574-1575. The provisions of Section 251 are to be liberally construed to allow the patentee to correct defects in the patent. In re Wilder, 736 F.2d 1516, 1519. In determining whether the scope of a reissued claim is broader than the original claim, the Court must view the reissued claim objectively from the perspective of a person of ordinary skill in the art. See e.g.

In re Amos, 953 F.2d 613, 618 (Fed. Cir. 1991).

Reviewing claim 11 of the '712 patent in light of claim 11 of the '590 upon which it is based, along with the specification of the '590 patent, the Court concludes that the correction made to claim 11 does not broaden the scope of the '712 patent beyond that which was originally claimed through the '590 patent. In reaching this conclusion, the Court credits the testimony of Dr. Klibanov that it would have been readily apparent to one of ordinary skill in the art that claim 11 of the '590 patent covered a stereoselective method for making substantially pure (+)-citalopram from a substantially pure form of the (-)-enantiomer of the Diol Intermediate and that claim 11 contained a typographical error in the optical rotation sign of the Diol Intermediate, the correction of which did not broaden the claim. (PTX 1017, Reaction Scheme II; PTX 1018, Example 2; Klibanov Tr. 1441:16-1442:4, 1443:21-1444:19, 1445:3-1446:22, 1448:15-1450:16, 1468:23-1469:3). As Dr. Klibanov explained, a person of ordinary skill in the art would use the technical examples and reaction schemes in the patent to understand its claims. (Klibanov 1467:19-1468:22). The specification of the '590 patent discloses two reaction schemes for the synthesis of (+)-citalopram from the Diol Intermediate, Reaction Scheme I and Reaction Scheme II. (Klibanov Tr. 1445:3-9, 1457:1-4). Of these two schemes, Defendants direct the Court to Reaction Scheme I and example 1 to

suggest ambiguity and conflict within the '590 patent in an effort to demonstrate that the correction made to claim 11 would not have been apparent to one of skill in the art. The Court, however, is not persuaded by Defendant's argument. Reaction Scheme I and example 1 are both silent as to which enantiomer of the Diol Intermediate gives rise to which enantiomer of citalopram, (Burke Tr. 471:3-474:2, 464:4-465:1; Klibanov Tr. 1454:1-1455:13, 1456:16-21, 1457:11-1458:5), and therefore, the Court is not persuaded that Reaction Scheme 1 and example 1 are as instructive in elucidating the meaning of claim 11 as Reaction Scheme II and claim 2. Further, Dr. Burke's assignment of the (+) sign to the Diol Intermediate in Reaction Scheme I presents an illogical scenario which directly contradicts what the specification provides for in Reaction Scheme II and creates the very conflicts which Dr. Burke purported to find in the '590 patent. (Klibanov Tr. 1462:5-1463:4, 1464:3-7; Burke Tr. 479:12-17). Moreover, Dr. Burke's assignment of the (+) sign without any instruction in the specification[8], and contrary to the very

[8] Dr. Burke testified that he based his conclusions on the language of claim 11 which used the (+) diol until it was corrected during the reissue. However, based on Dr. Burke's testimony, it is apparent to the Court that he used the claim language to rewrite the specification, which is contrary to the legal principles of claim interpretation. The specification is meant to illuminate the claims. Had Dr. Burke begun his analysis with the specification, the Court is persuaded that the use of the (+) sign in claim 11 would have been recognized for what it was, i.e. a typographical error.

examples contained within the specification, results in what one skilled in the art would know is a chemically impossible reaction. (Klibanov Tr. 1464:8-16, 1467:7-9; Burke Tr. 478:10-15; Bøgesø Tr. 1027:16-1028:2). Thus, the Court finds that Reaction Scheme I and example 1 lend little useful information in understanding the meaning of claim 11.

In contrast, Reaction Scheme II and example 2 elucidate the meaning of claim 11 by pointing out the correct optical rotation sign for the Diol Intermediate used in the synthesis of (+)-citalopram. Reaction Scheme II clearly shows that the (+) and (-) Diol Intermediates lead to (-) and (+) citalopram, respectively. (Klibanov Tr. 1446:2-7, 1446:14-22; 1448:4-1448:11). Example 2 is also consistent with Reaction Scheme II and clearly shows that (+)-citalopram is obtained from the (-)-Diol Intermediate. (Klibanov Tr. 1448:15-1450:16). Indeed, even Defendants' experts, Dr. Trost and Dr. Burke, acknowledged that a person of ordinary skill in the art would have understood that the invention being described in Scheme II and example 2 was the use of the minus Diol Intermediate to yield (+)-citalopram. (Burke Tr. 469:6-470:16; Trost Tr. 276:22-280:3). Because it would have been impossible as a matter of scientific fact to prepare (+)-citalopram from the (+) Diol Intermediate and the (-)-Diol Intermediate is the only designation that makes sense in light of the specification of the patent (Klibanov Tr. 1466:10-

1467:6), the Court concludes that reissue of the patent was necessary to correct a typographical mistake that was evident to one of ordinary skill in the art, and that the correction did not impermissibly broaden the scope of the '590 patent. See e.g. Slimfold Mfg. Co. v. Kinkead Indus., Inc., 810 F.2d 1113, 1116-1117 (Fed. Cir. 1987) (finding that correction during reissue of drafting error that examiner and patent attorney "could and probably should have spotted when the original patent was examined" did not alter the scope of the claims).

Relying on the Federal Circuit's decision in Superior Fireplace Company v. The Majestic Products Company, 270 F.3d 1358 (Fed. Cir. 2002), Defendants contend that the error sought to be corrected by a reissued patent must be apparent to the public and not to one of ordinary skill in the art. However, the Federal Circuit's decision in Superior Fireplace contemplates the use of 35 U.S.C. § 255 to make corrections that broaden the scope of the patent. In this case, the Court has concluded that the correction made to the '590 patent, reissued as the '712 patent, did not broaden the original claim, and therefore, the Court is not persuaded that the rationale of Superior Fireplace is applicable here. In this case, the correction made to the reissued claim makes the claim consistent with what is disclosed in the specification, and thus, it does not broaden the claim. Moreover, the Court's conclusion that the reissued patent did not

impermissibly broaden the original claims is further supported by the fact that the examiner allowed the reissued patent more than two years after the issue date of the original patent. Boyett v. St. Martin's Press, 884 F. Supp. 479, 785 (M.D. Fla. 1995) ("[A]lthough not binding, the Patent Examiner's decision to allow reissue [of the] claim . . . despite the passage of more than two years is an additional factor supporting a finding that the [d]efendants have not met their burden by clear and convincing evidence."). Indeed, the presumption of validity applies with equal force to reissued patents, see Kaufman Co. v. Lantech, Inc., 807 F.2d 970, 973-974 (Fed. Cir. 1986), and the Court is not persuaded that Defendants have overcome this presumption by clear and convincing evidence that the scope of the claim 11 was impermissibly broadened by the correction in the reissued patent.[9]

---

[9] In reaching this conclusion, the Court recognizes that a change in an optical rotation sign is not the type of "garden-variety" correction seen in cases involving typographical errors, and the Court acknowledges that, in some cases, such a change may be considered a more substantive change. However, in the context of this case, the Court is persuaded that the correction of the optical rotation sign should be characterized as the correction of a typographical error, rather than as a substantive error that affects the scope of the claim, because the correction of the error allows the patent to conform to what was described in the specification. In other words, given what the specification describes, the error is appropriately considered a typographical error.

II. Whether The '712 Patent Is Unenforceable As A Result Of Inequitable Conduct

A. Applicable Legal Principles

Pursuant to 37 C.F.R. § 1.56, individuals associated with the filing and prosecution of a patent application, including inventors named in the application, attorneys or agents prosecuting the application, and those involved in the preparation or prosecution of the application who are associated with the inventor, have a duty of candor, good faith and honesty in their dealings with the PTO. 37 C.F.R. 156(a), (c). The duty of candor, good faith and honesty includes the duty to submit truthful information to the PTO, as well as information which is material to the examination of the patent application. Elk Corp. of Dallas v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999). The duty of candor, good faith and honesty applies with equal force to those seeking reissue of a patent. Manual of Patent Examining Procedure § 1418.

Breach of the duty of candor, good faith and honesty may constitute inequitable conduct. Elk Corp., 168 F.3d at 30. A patent procured as a result of inequitable conduct may be unenforceable. Kingsdown Medical Consultants v. Hollister Incorporated, 863 F.2d 867, 877 (Fed. Cir. 1988).

To establish inequitable conduct due to the failure to disclose material information or the submission of false information, the party raising the issue must prove by clear and

convincing evidence that (1) the information is material; (2) the knowledge of this information and its materiality is chargeable to the patent applicant; and (3) the applicant's submission of false information or its failure to disclose this information resulted from an intent to mislead the PTO. Id. "Information is considered material when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." TAP Pharm. Prods. v. OWL Pharm., L.L.C., 419 F.3d 1346, 1351 (Fed. Cir. 2005). However, a reference that is material need not be disclosed if it is cumulative to or less material than other references that have already been disclosed. Elk Corp., 168 F.3d at 31. A reference is cumulative if it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1575 (Fed. Cir. 1997).

In addition to materiality, the party seeking to establish inequitable conduct must demonstrate that the patent applicant acted with the intent to deceive the PTO. The intent to deceive the PTO may be established by direct evidence or inferred from the facts and circumstances surrounding the applicant's overall conduct. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 (Fed. Cir. 1995). In determining whether the applicant's overall

conduct evidences an intent to deceive the PTO, the Federal Circuit has emphasized that the challenged "conduct must be sufficient to require a finding of deceitful intent in the light of all the circumstances." Kingsdown Medical Consultants, 863 F.2d at 873. Once materiality and intent have been established, the court must conduct a balancing test to determine "whether the scales tilt to a conclusion that 'inequitable conduct' occurred." Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997). Generally, the more material the omission, the less the degree of intent that must be shown to reach a conclusion of inequitable conduct. Elk Corp., 168 F.3d at 32.

The question of whether inequitable conduct occurred is equitable in nature. As such, the ultimate question of whether inequitable conduct occurred is committed to the sound discretion of the trial court. Elk Corp., 168 F.3d at 30-31; Kingsdown Medical Consultants, 863 F.2d at 876.

B. Whether Lundbeck Withheld Material Information From The PTO During The Prosecution Of The '712 Patent

In arguing that the '712 patent is unenforceable as a result of inequitable conduct, Defendants contend that Lundbeck withheld from the PTO three material references: (1) Smith (DTX 871); (2) A.F. Casy, Stereochemistry and Biological Activity, in Medicinal Chemistry 81-103 (Alfred Burger ed., John Wiley & Sons 3d ed., 1970) ("Burger") (DTX 637); and (3) M. Koreeda, et al.,

Communications to the Editor: Absolute Configuration of Natural (+)-Abscisic Acid, 95 J. Am. Chem. Soc'y 239 (1973) ("Koreeda") (DTX 727). Defendants contend that the Smith and Burger references were disclosed to the Danish Patent Office, and therefore, they were material references which should also have been disclosed to the PTO during the '712 reissue proceedings. Defendants also contend that the Koreeda reference teaches the separation of enantiomers using the method shown in Reaction Scheme I of the '712 patent and that this reference was noted in one of Lundbeck's laboratory notebooks. Thus, Defendants contend that Koreeda was a material reference which should have been disclosed to the PTO.

In connection with the '712 reissue application, Lundbeck provided the PTO with the '193 patent disclosing racemic citalopram and the '884 patent covering the racemic diol intermediate and the process for making citalopram from the racemic diol intermediate. The parties appear to agree that the '193 patent is the closest prior art reference to the '712 patent. In light of these disclosures, and in the context of the record as a whole, the Court has considered the Smith, Burger and Koreeda references and concludes that Defendants have failed to establish that Lundbeck intentionally deceived the PTO by failing to disclose these references during the '712 reissue proceedings. As the Court discussed in the context of anticipation, the Smith

reference does not disclose (+)-citalopram in substantially pure form, and the Smith reference describes no methods for separating citalopram into its enantiomers. In addition, Smith incorrectly predicted that the (R)-enantiomer of citalopram would be more potent than the (S)-enantiomer, and in this regard, Smith actually taught away from the claimed invention. (See e.g., Trost Tr. 260:4-262:12; Barker Tr. 421:23-422:11; Smith Tr. 1151:4-18). Further, Smith was disclosed in the '193 patent, and in the Court's view, the Smith reference is certainly less material than the '193 patent itself. Accordingly, the Court concludes that the Smith reference was either immaterial to the claimed invention, cumulative to that which was already known in the art disclosed to the PTO, or less material than that which was already disclosed to the PTO, and therefore, the Smith reference was not required to be disclosed to the PTO in connection with the '712 reissue application.

As for the Burger reference, the Court notes that Burger was disclosed before the Danish Patent Office and was cited by the Danish Patent Office in rejecting claims 1 through 5 of the counterpart to the '712 patent, which claimed (+)-citalopram. However, it is not clear to the Court that Burger was cited by the Danish Patent Office as an invalidating reference in and of itself. Rather, it appears to the Court that the Danish Patent Office cited Burger as an example of the state of the art to

demonstrate that it was already well known in the art that one enantiomer in a given pair might be more or less potent than the other enantiomer. (DTX 16 at 115). Indeed, Dr. Bøgesø and the experts on both sides have acknowledged that Burger makes no statements as to citalopram specifically and only states that which was already known in the art, i.e. that one enantiomer may be more or less potent than another. In this regard, Defendants have not demonstrated to the Court by clear and convincing evidence that Burger was a material reference. However, even if Burger can be considered material, the Court concludes that Defendants have failed to demonstrate by clear and convincing evidence that anyone with a duty to the PTO intended to deceive the PTO by failing to disclose the reference. Indeed, Dr. Bøgesø admitted that he was well-aware of the Burger reference, but he considered it to be common knowledge to one skilled in the art and his testimony does not evidence an intent to deceive the PTO by withholding what he considered to be common knowledge. (Barker 410:21-24; Bøgesø Tr. 1009:22-1010:11, 1017:13-20).

Similarly, with regard to the Koreeda reference, the Court concludes that Defendants have not demonstrated by clear and convincing evidence that the reference was material or that anyone with a duty of candor to the PTO was aware of it. Koreeda was not cited in either the Danish prosecution of the '590 patent or to the PTO during the prosecution of the reissued '712 patent.

The record contains only a brief description of Koreeda by Dr. Trost, and Dr. Trost did not explain how Koreeda was material to the claimed invention of the '712 patent. In fact, when asked to point to a reference disclosing the type of reaction set forth in the '712 patent involving an enantioconserving cyclization reaction of a diol containing a tertiary amine, Dr. Trost did not refer to Koreeda, even though he had discussed it in his earlier testimony. (Tr. 274:20-275:8). Defendants point out that Koreeda was noted in a laboratory book of a laboratory assistant; however, Defendants have not established that the assistant had a duty of candor to the PTO or that anyone with such a duty was aware of the reference.

Defendants urge the Court to find deceptive intent based upon a pattern of non-disclosure; however, the Court does not believe such a pattern exists in this case. First, the Smith reference is not material, and therefore, the Court is not persuaded that the nondisclosure of Smith should go to any attempt to establish a pattern of deception. Second, there is no evidence that Koreeda was known to anyone with a duty of candor to the PTO. Thus, the Court is left with the Burger reference, which Defendants have also failed to establish was a material reference that was intentionally withheld. However, even if Burger can be said to be a material reference of which the inventor was aware, the Court cannot find a pattern suggestive of

deceptive intent based on a single instance of nondisclosure. Accordingly, the Court concludes that Defendants have not demonstrated that Lundbeck intentionally withheld material references from the PTO with an intent to deceive the patent examiner.

C. Whether Lundbeck Made False Statements To The PTO

Defendants next contend that Lundbeck made false and material statements to the PTO. Specifically, Defendants contend that Lundbeck falsely stated to the PTO in prosecuting the '590 patent that "[r]esults upon administration [of (+)-citalopram] to human being [sic] have been very gratifying;" when in truth, the '590 patent had not yet been administered to humans as of the filing date of its application. (DTX 3 at FL-PAT000257, Col. 8:52-54).

Reviewing the record as it pertains to this misstatement, the Court concludes that Defendants have not demonstrated that the statement was material to patentability or made intentionally to deceive the PTO. Defendants suggest that a reasonable patent examiner would consider human studies to be important in determining whether to issue a patent; however, the Court is not persuaded that a general, self-serving statement of "gratifying" results, without any specific scientific data, is the type of information that a reasonable patent examiner would consider important to patentability. Indeed, the evidence demonstrates

that, in granting the '590 patent, the examiner did not rely upon this general statement of gratifying human test results, and instead expressly relied upon the specific data for rat studies regarding the improved pharmacological properties of (+)-citalopram. (DTX 4 at FL-PAT000307-311, Notice of Allowance of '590 Patent). Further, the statement of human testing was removed from the '712 patent during the reissue proceedings, and its removal was not commented upon by the patent examiner. In the Court's view, the lack of comment further demonstrates that the statement identified by Defendants was not the type of statement that would be considered important to a reasonable patent examiner. (DTX 1, 2). Further, Defendants have not established that Lundbeck intended to deceive the PTO in making this statement. (Bøgesø Tr. 1055:17-20). Indeed, the error initially went unnoticed by Dr. Bøgesø[10], but when it was discovered, it was corrected voluntarily during the reissue proceedings which suggests good faith on the part of Plaintiffs. (Bøgesø Tr. 1053:15-1056:19; DTX 1); Purdue Pharma L.P. v. Endo

---

[10] See e.g. Kingsdown Med. Consultants Ltd. v. Hollister Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (recognizing that "a finding that particular conduct amounts to 'gross negligence' does not of itself justify an inference of an intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive. . . ."); N.V. Akzo v. E.I. Dupont de Nemours, 810 F.2d 1148, 1153 (Fed. Cir. 1987) ("Simple negligence . . . or an error in judgment is never sufficient for a holding of inequitable conduct).

Pharm. Inc., 438 F.3d 1123, 1134 (Fed. Cir. 2006) ("When determining whether intent has been shown, a court must weigh all evidence, including evidence of good faith."). Accordingly, the Court is not persuaded that Defendants have established, by clear and convincing evidence, that Lundbeck intended to deceive the PTO with the misstatement concerning human studies.

Defendants also contend that Lundbeck misrepresented to the PTO that it was surprised that almost all of the activity of citalopram resided in one enantiomer. Plaintiffs have not responded to Defendants argument concerning this alleged misstatement; however, the Court is not persuaded that the statement is false or material. In pertinent part, the '712 patent states that "it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer." DTX 1 at FL-PAT00002, Col. 2:40-42. Defendants contend that it was known in the art that one of the enantiomers would be more active than the other, and therefore, Lundbeck made a false statement of surprise. However, none of the prior art references to which Defendants refer indicate that the activity would be in (+)-citalopram. In fact, the Smith reference predicts exactly the opposite. Thus, the Court cannot conclude that Lundbeck's statement of surprise that the activity of citalopram resided in the (+)-citalopram enantiomer is false.

Further, the Court is not persuaded that Lundbeck's statement is material. Specifically, Defendants contend that "Lundbeck's false claim of surprise was material because enantiomers are prima facie obvious in view of their racemates." (D.I. 603 at 188). However, as Defendants acknowledge, Lundbeck disclosed racemic citalopram in the '193 patent, and as the Court has discussed in the context of both anticipation and obviousness, disclosure of a racemate does not necessarily render its isomers obvious. See e.g. Pfizer, 405 F. Supp. 2d at 519. Accordingly, the Court is not persuaded that the '712 patent's statement of surprise at the activity of (+)-citalopram is a false or material misstatement upon which to base a finding of inequitable conduct.

D. Summary

In sum, the Court concludes that Defendants have not established that the '712 patent is unenforceable as a result of inequitable conduct. First, Defendants have failed to establish that the references and alleged misstatements are material. In addition, Defendants have failed to establish by clear and convincing evidence that Plaintiffs intended to mislead the PTO. Further, even if such an intent to mislead was shown with respect to a material reference, the Court is not persuaded that the circumstances of this case warrant a finding of inequitable conduct. Defendants have not demonstrated a pattern of

deception, and the closest prior art to the '712 patent was disclosed during the reissue proceedings. Accordingly, the Court concludes that Defendants have not provided the Court with sufficient evidence to tilt the scales in favor of a finding of inequitable conduct, and therefore, the Court will enter judgment in favor of Plaintiffs and against Defendants on Defendants' counterclaim that the '712 patent is unenforceable as a result of inequitable conduct.

CONCLUSION

For the reasons discussed, the Court concludes that Defendants have not established that the '712 patent is invalid as anticipated, obvious or impermissibly broadened upon reissue. The Court further concludes that Defendants have not established that the '712 patent is unenforceable as a result of inequitable conduct. Accordingly, the Court will enter judgment in favor of Plaintiffs and against Defendants on Defendants' counterclaims of invalidity and unenforceability of the '712 patent.

Plaintiffs shall submit a proposed Final Judgment Order to the Court, with notice to Defendants, no later than July 21, 2006.